

Screening and baseline characteristics of a Ph2B/3 randomized, placebo-controlled trial of emestedastat in mild/moderate AD



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Background

Emestedastat is an oral, selective 11 β -HSD1 inhibitor that decreases brain cortisol. Clinical trials of a 10mg daily dose have demonstrated adequate target engagement and/or clinical benefit by PET imaging, antidepressant activity, improvements in cognitive performance in healthy older adults, and attenuation of CDR-SB decline in pTau181-elevated clinically diagnosed Alzheimer's Disease (AD) patients (Fig. 1).

As shown in Fig. 1, and by other groups ptau181 selects for progressive AD

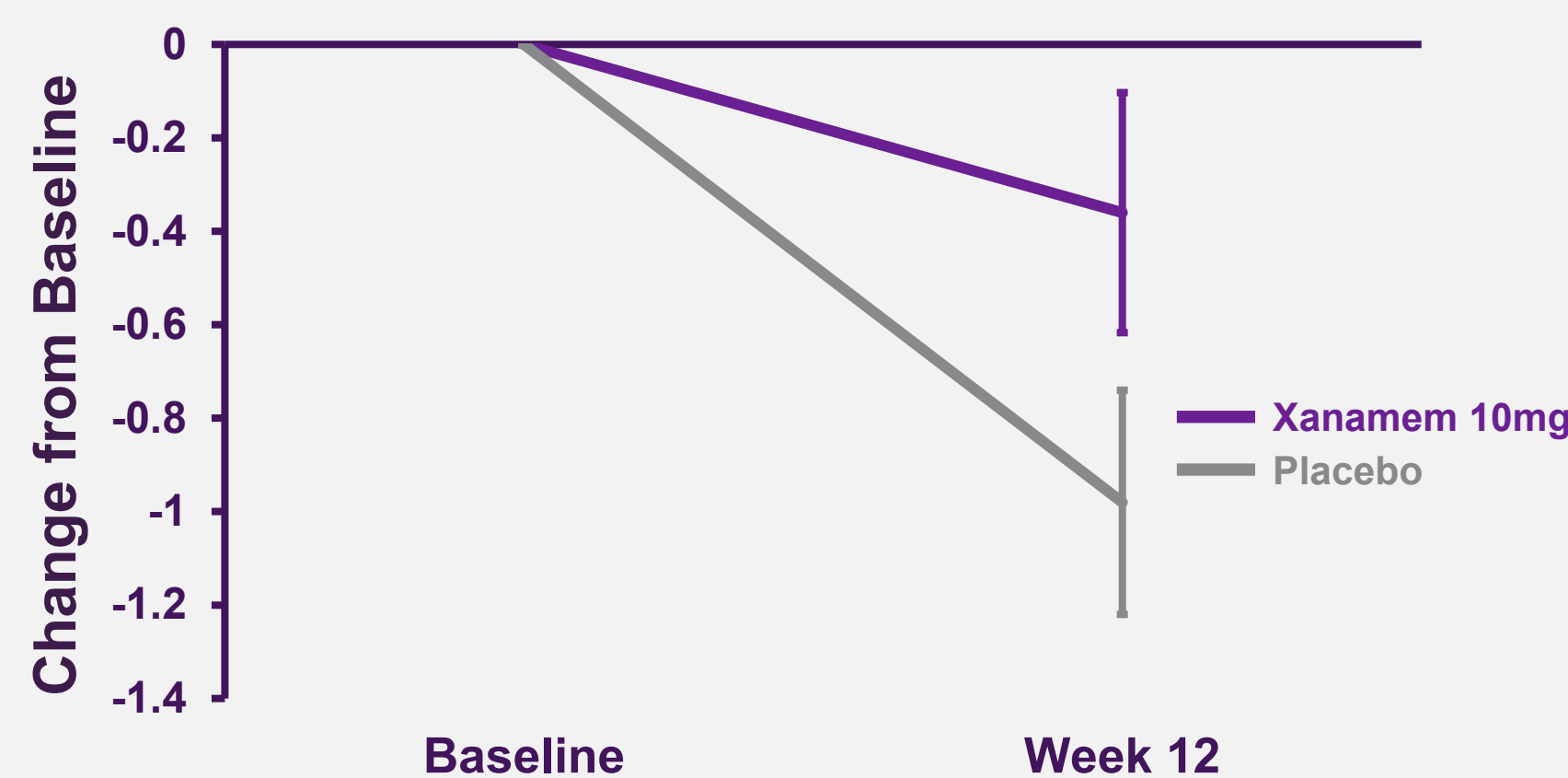


Fig 1: CDR-SB change from baseline scores over 12-week treatment period in previous Phase 2 randomised trial. In patients with a clinical diagnosis of AD and elevated plasma pTau181, 10mg daily emestedastat was associated with a slower mean rate of CDR-SB decline (0.36) vs placebo (0.98; Cohen's d=0.41, p=0.09).

Methods

XanaMIA is a multicentre, double-blind, randomised, placebo-controlled Phase 2B/3 trial in mild to moderate AD.

Inclusion criteria include age ≥ 50 , CDR global score 0.5-1.0, MMSE 18-26, and elevated plasma pTau181 (≥ 1.6 pg/ml; LumiPulse). Stable symptomatic AD medications were allowed. Participants were randomised 1:1 to daily emestedastat 10mg or placebo for 36 weeks, with 4 weeks blinded follow up.

The trial used a 2-staged screening process comprising a pre-screening visit followed by a screening visit. The primary purpose of the pre-screening was to exclude participants without elevated pTau181 early to improve efficiency and reduce participant screening burden.

The primary endpoint is change from baseline to Week 36 in CDR-SB. Key secondary endpoints include a digital cognitive test battery (CTB) assessing global cognition and the Amsterdam Instrumental Activities of Daily Living (A-iADL). Emestedastat's effect on plasma biomarkers of AD (pTau181, pTau217), neurodegeneration (NfL, GFAP), other markers of neuroinflammation will also be evaluated.

Demographics and baseline characteristics

Age (yrs) mean (SD), min to max	74.5 (8.0), 50 to 91
Sex n (%)	
Male	126 (51.0)
Female	121 (49.0)
Country enrolled (%)	
Australia	111 (44.9)
USA	136 (55.1)
Race n (%)	
White	233 (94.3)
Black / African American	6 (2.4)
Asian	4 (1.6)
Other	4 (1.6)
APOE* n (%)	
e2/e3	8 (3.3)
e2/e4	7 (2.9)
e3/e3	66 (27.3)
e3/e4	119 (49.2)
e4/e4	41 (16.9)
Concomitant AD medication n (%)	
Donepezil	107 (43.3)
Galantamine	8 (3.2)
Rivastigmine	9 (3.6)
Memantine	43 (17.4)
MMSE mean (SD)	21.8 (3.25)
CDR-Global mean (SD)	0.73 (0.33)
CDR-SB mean (SD)	4.3 (1.95)
pTau181 pg/mL mean (SD)	2.55 (1.33)
median (range)	2.31 (1.60 to 18.6) [†]

[†] 18.6 pg/mL is an outlier

Participant flow with staged screening approach

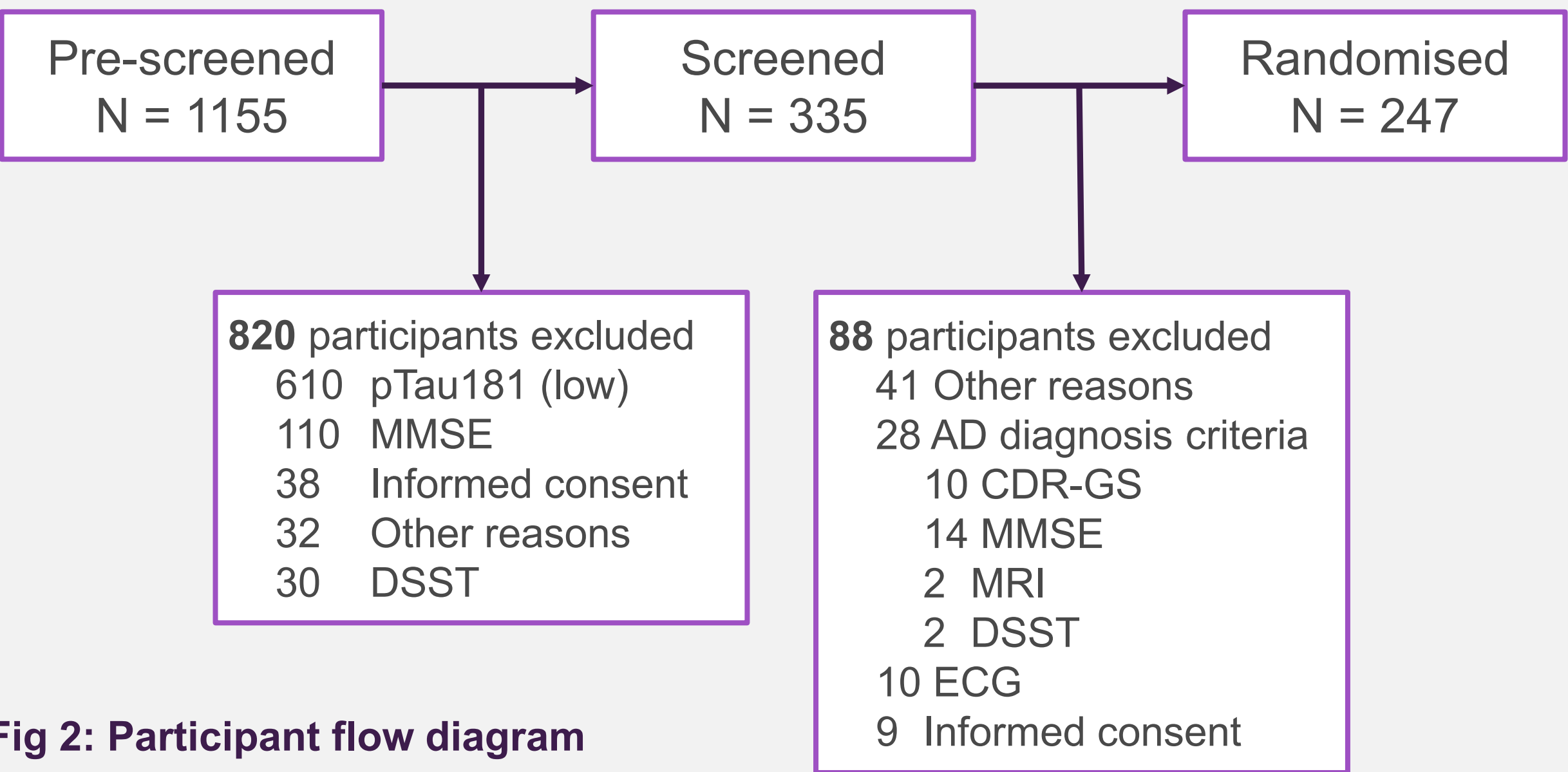


Fig 2: Participant flow diagram

Reducing cost and patient burden

The XanaMIA trial's 2-staged screening approach improved trial efficiency. By excluding participants with low pTau181 at the pre-screening visit, a total of 819 full patient screening visits were saved. This equates to a 42.9% reduction in screening costs compared to a single screening visit approach (Fig. 3).

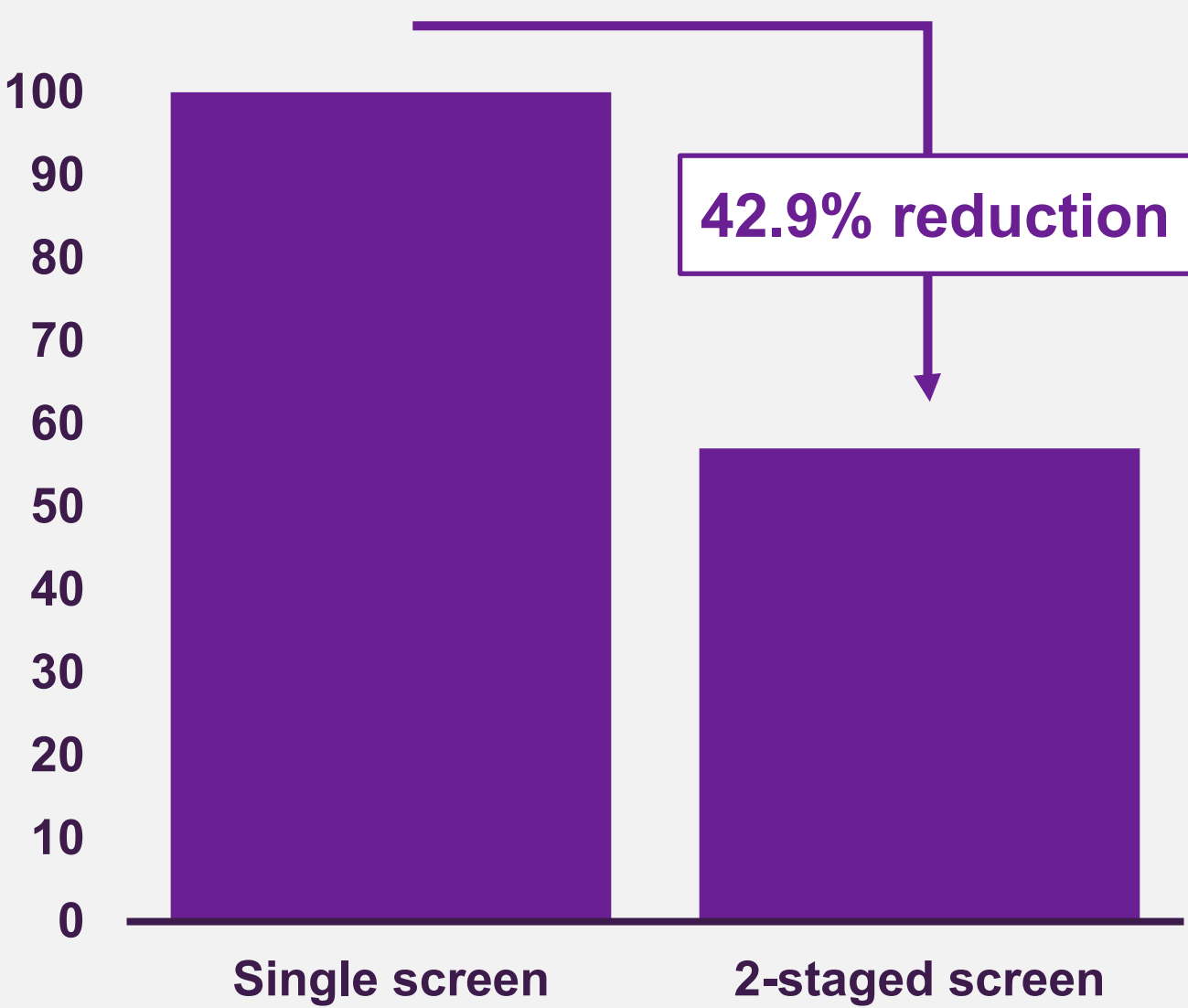


Fig 3: % cost reduction of a 2-staged screening approach compared to a single screening visit. Average site costs for the pre-screening and screening visits were used.

Conclusions

- ✓ A 2-staged method improved screening efficiency in this contemporary AD trial
- ✓ Plasma pTau181 selects for a progressive AD population ideal for evaluating potential emestedastat benefits over 36-weeks
- ✓ The enrolled population is typical for a mild / moderate AD population
- ✓ Topline results are expected in November 2026

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